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Brian C. Remy
(Print Name)

Date: May 9, 2005

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Group: 1624

Konrad Honold, et al.

Serial No.: 10/809,067

Filed: March 25, 2004

For: **PYRIDO[2,3-D]PYRIMIDIN-7-CARBOXYLIC ACID DERIVATIVES, THEIR MANUFACTURE AND USE AS PHARMACEUTICAL AGENTS**

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May 9, 2005

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Dear Sir:

Attached please find two certified copies of the foreign application from which priority is claimed for this case:

Country	Application No.	Filing Date
Europe	03007182.3	March 28, 2003

Respectfully submitted,

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Enclosure
156028

Europäisches Patentamt	European Patent Office	Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03007182.3

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 03007182.3
Demande no:

Anmeldetag:
Date of filing: 28.03.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Novel pyrido[2,3-d]pyrimidin-7-carboxylic acid derivatives, their manufacture and use as pharmaceutical agents

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D471/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR LI

Novel pyrido[2,3-d]pyrimidin-7-carboxylic acid derivatives, their manufacture and use as pharmaceutical agents

The present invention relates to novel, bicyclic pyrido[2,3-d]pyrimidines, to a process for their manufacture, medicaments containing them and their manufacture as well as the use of these compounds as pharmaceutically active agents.

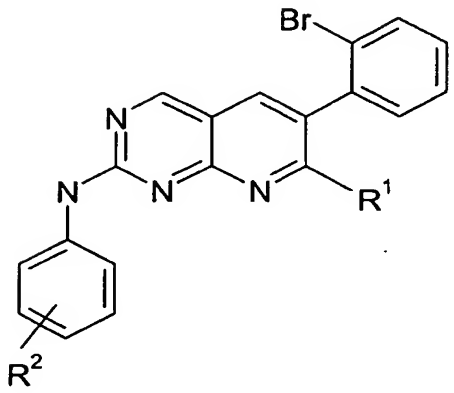
Some substituted bicyclic nitrogen heterocycles are known in the art for their protein kinase, as well as their tyrosine kinase inhibitory activity. WO 02/090360 discloses pyrido[2,3-d]pyrimidines useful as kinase enzyme inhibitors and for the treatment of hyperproliferative diseases.

WO 03/000011 discloses phosphorus-containing derivatives of pyrido[2,3-d]pyrimidine as protein kinase inhibitors and for the treatment of bone disorders, cancer and signalling disorders in general.

WO 96/15128 discloses 6-aryl-pyrido[2,3-d]pyrimidines as inhibitors of protein tyrosine kinases and for the treatment of atherosclerosis, restenosis, psoriasis, bacterial infections and cancer.

Despite the progress documented in the above-mentioned literature, there remains a need for new compounds with an improved therapeutic index, such as improved activity, tolerability, selectivity or stability to name only a few.

The present derivatives are new compounds of the general formula



(formula I),

wherein

R^1 is -C(O)-NH-alkyl or -C(O)-N(alkyl)$_2$, which alkyl groups are optionally substituted with

-OH;
-NH(alkyl);
-N(alkyl)$_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-N(alkyl)$_2$;
-C(O)-NH$_2$;
-O-alkyl;
-heterocyclyl;
-NH-heterocyclyl;
-S(O)$_2$-NH$_2$; or
-S(O)-alkyl, which alkyl is optionally substituted with -OH;

or a group

-CN;
-C(O)-NH$_2$;
-C(O)-NH-heterocyclyl;
-C(O)-NH-NH-C(O)-NH$_2$; or
-C(O)-NH-NH-C(O)-alkyl, which alkyl is optionally substituted with

-NH(alkyl); or

$-N(alkyl)_2$; and

R^2 is halogen;
heterocyclyl;
$-(CH_2)_m-S(O)_2-NH_2$;
$-(CH_2)_m-S(O)_2-N(alkyl)_2$; or
$-(CH_2)_m-S(O)_2-NH-(alkyl)$;
-O-alkyl; or
$-S(O)_n$-alkyl, which alkyl groups are optionally substituted by
-OH;
$-O-(C_1-C_4)$alkyl;
-NH-alkyl; or
$-N(alkyl)_2$;

m is 0, 1, 2, 3, 4, 5 or 6;
n is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

The compounds according to this invention show activity as protein kinase inhibitors, in particular src family tyrosine kinase inhibitors, and may therefore be useful for the treatment of diseases mediated by said tyrosine kinases. The family of tyrosine kinases plays an important role in the regulation of cell signaling and cell proliferation by phosphorylating tyrosine residues of peptides and proteins. Inappropriate activation of tyrosine kinases is known to be involved in a variety of disease states including inflammatory, immunological, CNS disorders, or oncological disorders, or bone diseases. See for example Susa, M., et al., Trends Pharmacol. Sci., 21 (2000) 489-495; Biscardi, J.S., et al., Adv. Cancer Res. 76 (2000) 61-119.

Compounds of the present invention may be used as active agents in the prevention and therapy of, for example, transplant rejection, inflammatory bowel syndrome, rheumatoid arthritis, psoriasis, restenosis, allergic asthma, Alzheimers disease, Parkinson, stroke, osteoporosis, cancer, and benign hyperplasias.

The compounds of the present invention have surprisingly been found to show improved metabolic stability and / or selectivity, together with at least the same activity against src-tyrosine kinase compared to compounds known in the art.

Objects of the present invention are the compounds of formula I and pharmaceutically acceptable salts and their enantiomeric forms, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders as mentioned above or in the manufacture of corresponding medicaments.

As used herein, the term "alkyl" means a saturated, straight-chain or branched-chain hydrocarbon containing from 1 to 6, preferably from 1 to 4, carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, t-butyl, n-pentyl, n-hexyl as well as their isomers. "Optionally substituted" alkyl groups are alkyl groups as defined above, which are either unsubstituted or one or, if possible, two times substituted.

As used herein, the term "(C_1-C_4)alkyl" means a saturated, straight-chain or branched-chain hydrocarbon containing from 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, t-butyl.

The term "heterocyclyl" as used herein means a 5 to 8 membered, mono- or bicyclic, aromatic or non-aromatic hydrocarbon, wherein 1 to 3, preferably 1 or 2, carbon atoms are replaced by a nitrogen-, oxygen- or sulphor atom. Said heterocyclyl group is optionally substituted once or several times with alkyl, oxo or $-C(O)-NH_2$. Examples are 2-oxo-imidazolidin-1-yl; pyrrolidin-2-yl; pyrrolidin-3-yl; 2-oxo-pyrrolidin-1-yl; 1-methyl-pyrrolidin-2-yl; imidazol-4-yl; pyrazol-3-yl; 2-methyl-pyrazol-3-yl; 1-methyl-pyrazol-5-yl; 1,5-dimethyl-pyrazol-3-yl; 4-carbamoyl-pyrazol-3-yl; piperidin-3-yl; piperidin-4-yl; 1-methyl-piperidin-4-yl; morpholin-4-yl; pyridin-2-yl or 1-aza-bicyclo[2.2.2]oct-3-yl.

Preferably the substituent R^2 in formula I is located in para or meta position.

An embodiment of the invention are the compounds of formula I, wherein

R^1 has the significance given above, and

R^2 is halogen;

and pharmaceutically acceptable salts thereof.

Another embodiment of the invention are the compounds of formula I, wherein

R^1 has the significance given above, and

R^2 is morpholin-4-yl;
-S-alkyl; or a group
-O-alkyl, which alkyl group is substituted with
-N(alkyl)$_2$;

and pharmaceutically acceptable salts thereof.

Another embodiment of the invention are the compounds of formula I, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is substituted with
-OH;
-NH(alkyl);
-N(alkyl)$_2$; or
-S(O)$_2$-NH$_2$;

or a group

-C(O)-NH-piperidin-3-yl;
-C(O)-NH-pyrrolidin-3-yl;
-C(O)-NH-CH$_2$-pyrrolidin-2-yl; or
-C(O)-NH-(CH$_2$)$_2$-imidazol-4-yl; and

R^2 is morpholin-4-yl;
-S-alkyl;
-O-alkyl, which alkyl group is substituted with
-N(alkyl)$_2$; or
-S(O)$_2$-NH-alkyl, which alkyl group is substituted with
-OH; or
-O-(C$_1$-C$_4$)alkyl;

and pharmaceutically acceptable salts thereof.

Preferred are the compounds of formula I, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is substituted with
-OH;
-NH(alkyl);
-N(alkyl)$_2$; or
-S(O)$_2$-NH$_2$; and

R^2 is morpholin-4-yl;

and pharmaceutically acceptable salts thereof.

Also preferred are the compounds of formula I, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is substituted with
-OH;
-NH(alkyl);
-N(alkyl)$_2$; or
-S(O)$_2$-NH$_2$; and

R^2 is -S-alkyl;

and pharmaceutically acceptable salts thereof.

Also preferred are the compounds of formula I, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is substituted with
-OH;
-NH(alkyl);
-N(alkyl)$_2$; or
-S(O)$_2$-NH$_2$; and

R^2 is -O-alkyl, which alkyl group is substituted with
-N(alkyl)$_2$;

Further preferred are the compounds of formula I, wherein

R^1 is -C(O)-NH-piperidin-3-yl;
-C(O)-NH-pyrrolidin-3-yl;
-C(O)-NH-CH_2-pyrrolidin-2-yl; or
-C(O)-NH-$(CH_2)_2$-imidazol-4-yl; and

R^2 is -O-alkyl, which alkyl group is substituted with
-N(alkyl)$_2$;

and pharmaceutically acceptable salts thereof.

Further preferred are the compounds of formula I, wherein

R^1 is -C(O)-NH-piperidin-3-yl;
-C(O)-NH-pyrrolidin-3-yl;
-C(O)-NH-CH_2-pyrrolidin-2-yl; or
-C(O)-NH-$(CH_2)_2$-imidazol-4-yl; and

R^2 is -$S(O)_2$-NH-alkyl, which alkyl group is substituted with
-OH; or
-O-(C_1-C_4)alkyl;

and pharmaceutically acceptable salts thereof.

Further preferred are the compounds of formula I, wherein

R^1 is -CN;
R^2 is morpholin-4-yl;
-S-alkyl;
-O-alkyl, which alkyl group is substituted with
-N(alkyl)$_2$; or
-$S(O)_2$-NH-alkyl, which alkyl group is substituted with
-OH; or
-O-(C_1-C_4)alkyl;

and pharmaceutically acceptable salts thereof.

Also preferred are the compounds of formula I, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is substituted with
-OH;
-NH(alkyl);
-N(alkyl)$_2$; or
-S(O)$_2$-NH$_2$; and

R^2 is -S(O)$_2$-NH-alkyl, which alkyl group is substituted with
-OH; or
-O-(C_1-C_4)alkyl;

and pharmaceutically acceptable salts thereof.

Further preferred are the compounds of formula I, wherein

R^1 is -C(O)-NH-piperidin-3-yl;
-C(O)-NH-pyrrolidin-3-yl;
-C(O)-NH-CH_2-pyrrolidin-2-yl; or
-C(O)-NH-(CH_2)$_2$-imidazol-4-yl; and

R^2 is morpholin-4-yl;

and pharmaceutically acceptable salts thereof.

Further preferred are the compounds of formula I, wherein

R^1 is -C(O)-NH-piperidin-3-yl;
-C(O)-NH-pyrrolidin-3-yl;
-C(O)-NH-CH_2-pyrrolidin-2-yl; or
-C(O)-NH-(CH_2)$_2$-imidazol-4-yl; and

R^2 is -S-alkyl;

and pharmaceutically acceptable salts thereof.

and pharmaceutically acceptable salts thereof.

Still another embodiment of the invention are the compounds of formula I, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is optionally substituted with
-OH;
-NH(alkyl);
-N(alkyl)$_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-N(alkyl)$_2$;
-C(O)-NH$_2$;
-O-alkyl;
-S(O)-alkyl, which alkyl is optionally substituted with -OH;
or
-S(O)$_2$-NH$_2$; and

R^2 is halogen;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methoxy-ethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-dimethylamino-propyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-dimethylamino-2,2-dimethyl-propyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-acetylamino-ethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methylamino-ethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid carbamoylmethyl-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-1-methyl-ethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid methylcarbamoylmethyl-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-propyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid dimethylcarbamoylmethyl-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-methylamino-propyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-sulfamoyl-ethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-hydroxy-propyl)-amide;

(S)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2,3-dihydroxy-propyl)-amide;

(R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2,3-dihydroxy-propyl)-amide

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfinyl-ethyl)-amide; or

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(2-hydroxy-ethanesulfinyl)-ethyl]-amide.

Yet another embodiment of the invention are the compounds of formula I, wherein

R^1 is -C(O)-N(CH_3)alkyl, which alkyl group is optionally substituted with
-NH(alkyl);
-N(alkyl)$_2$; and

R^2 is halogen;

and pharmaceutically acceptable salts thereof.

Such a compound is for example:

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide.

Yet another embodiment of the invention are the compounds of formula I, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is substituted with
morpholin-4-yl;
pyrrolidinyl;
2-oxo-imidazolidinyl;
2-oxo-pyrrolidinyl;
1-methyl-pyrrolidinyl;
3H-imidazolyl;
1,5-dimethyl-pyrazolyl; or
-NH-pyridinyl;

R^2 is halogen;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide;

(R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (pyrrolidin-2-ylmethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-morpholin-4-yl-propyl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(pyridin-2-ylamino)-ethyl]-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(3H-imidazol-4-yl)-ethyl]-amide; or

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1,5-dimethyl-1H-pyrazol-3-ylmethyl)-amide.

Yet another embodiment of the invention are the compounds of formula I, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is substituted with
-NH-alkyl;
-$N(alkyl)_2$; or
-C(O)-NH-piperidin-4-yl; and

R^2 is morpholin-4-yl;
-S-alkyl; or
-O-alkyl, which alkyl group is substituted with
-$N(alkyl)_2$;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

6-(2-Bromo-phenyl)-2-(3-methylsulfanyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide;

6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methylamino-ethyl)-amide;

6-(2-Bromo-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide; or

6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-4-ylamide.

Yet another embodiment of the invention are the compounds of formula I, wherein

R^1 is -C(O)-NH-heterocyclyl;
-C(O)-NH-NH-$C(O)-NH_2$; or
-C(O)-NH-NH-C(O)-alkyl, which alkyl is optionally substituted with
-NH(alkyl); or
-$N(alkyl)_2$;

R^2 is halogen;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

(R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-3-ylamide;

(S)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-3-ylamide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-4-ylamide;

1-[6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonyl]semicarbazide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid N'-(2-dimethylamino-acetyl)-hydrazide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1-methyl-piperidin-4-yl)-amide;

(S)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid pyrrolidin-3-ylamide;

(R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid pyrrolidin-3-ylamide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1-aza-bicyclo[2.2.2]oct-3-yl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1H-pyrazol-3-yl)-amide;

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methyl-2H-pyrazol-3-yl)-amide; or

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (4-carbamoyl-1H-pyrazol-3-yl)-amide.

Yet another embodiment of the invention are the compounds of formula I, wherein

R^1 is $-C(O)-NH_2$; and

R^2 is morpholin-4-yl;
$-(CH_2)_m-S(O)_2-NH-(alkyl)$;
$-(CH_2)_m-S(O)_2-NH_2$; or a group
-O-alkyl, $-S(O)_n$-alkyl, which alkyl groups are optionally substituted by
-OH;
-NH-alkyl; or
$-N(alkyl)_2$;

m is 0, 1, 2, 3, 4, 5 or 6;

n is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide;

6-(2-Bromo-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide;

6-(2-Bromo-phenyl)-2-(3-methylsulfanyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide;

6-(2-Bromo-phenyl)-2-(4-sulfamoyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide;

6-(2-Bromo-phenyl)-2-(3-methylsulfamoylmethyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide;

6-(2-Bromo-phenyl)-2-[3-(2-hydroxy-ethanesulfonyl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide; or

6-(2-Bromo-phenyl)-2-(3-methanesulfonyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide.

Yet another embodiment of the invention are the compounds of formula I, wherein

R1 is -CN; and

R2 is morpholin-4-yl;
-$S(O)_n$-alkyl; or a group
-O-alkyl, which alkyl group is optionally substituted by
-OH;
-NH-alkyl;
-$N(alkyl)_2$;

n is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile; compound with trifluoro-acetic acid;

6-(2-Bromo-phenyl)-2-(3-methanesulfonyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile;

6-(2-Bromo-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile;

6-(2-Bromo-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile;

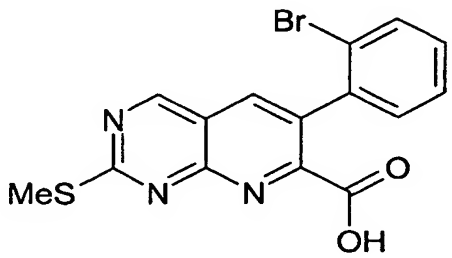
6-(2-Bromo-phenyl)-2-[4-(2-ethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile;

6-(2-Bromo-phenyl)-2-(3-methanesulfinyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile; or

6-(2-Bromo-phenyl)-2-[3-(2-hydroxy-ethanesulfonyl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile.

Still another embodiment of the invention is a process for the manufacture of the compounds according to this invention, wherein

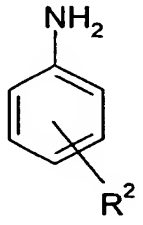
(a) the sulfide group in the compounds of the general formula (II)



formula (II),

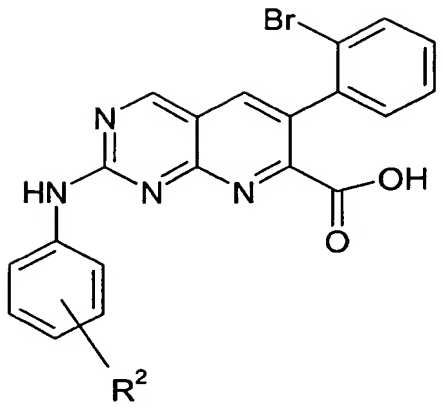
is converted into the corresponding sulfoxide group, which sulfoxide group is

(b) substituted by the respective anilines of formula (II-A)



formula (II-A)

wherein R^2 has the meaning given herein before, to give the compounds of the general formula (IV)



formula (IV),

(c) the -COOH group in formula (IV) is converted into an amide derivative of formula (I); and

(d) if desired a primary amide derivative obtained from (c) is further converted into its corresponding 7-carbonitril derivative of formula (I); and

(e) if desired said compound of the general formula (I), obtained from (c) or (d), is converted into a pharmaceutically acceptable salt.

In a more detailed description, the compounds of formula (I) wherein R^1 is attached via an amid group are represented by the general formula (Ia). Such compounds can be prepared from the carboxylic acids of formula (II), using standard reactions well known to the one skilled in the art. The synthesis of the compounds of the general formula (Ia) is shown in scheme 1, wherein R^3 has the significance given above for R^1 without the group –CN, therefore

R^3 is -C(O)-NH-alkyl or -C(O)-N(alkyl)$_2$, which alkyl groups are optionally substituted with

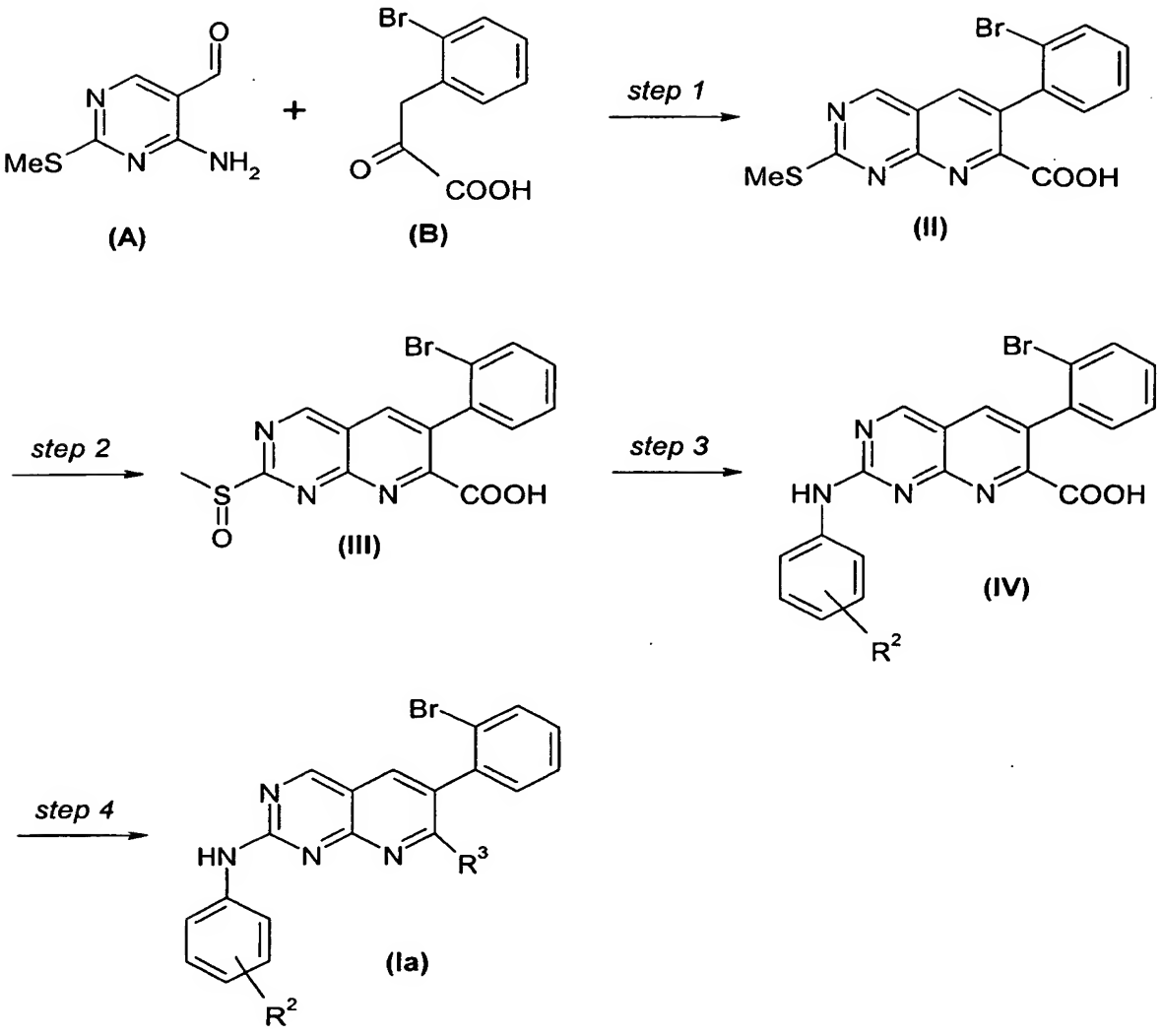
-OH;
-NH(alkyl);
-N(alkyl)$_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-N(alkyl)$_2$;

-C(O)-NH_2;
-O-alkyl;
-heterocyclyl;
-NH-heterocyclyl;
-$S(O)_2$-NH_2; or
-S(O)-alkyl, which alkyl is optionally substituted with -OH;

or a group
-C(O)-NH_2;
-C(O)-NH-heterocyclyl;
-C(O)-NH-NH-C(O)-NH_2; or
-C(O)-NH-NH-C(O)-alkyl, which alkyl is optionally substituted with
-NH(alkyl); or
-$N(alkyl)_2$;

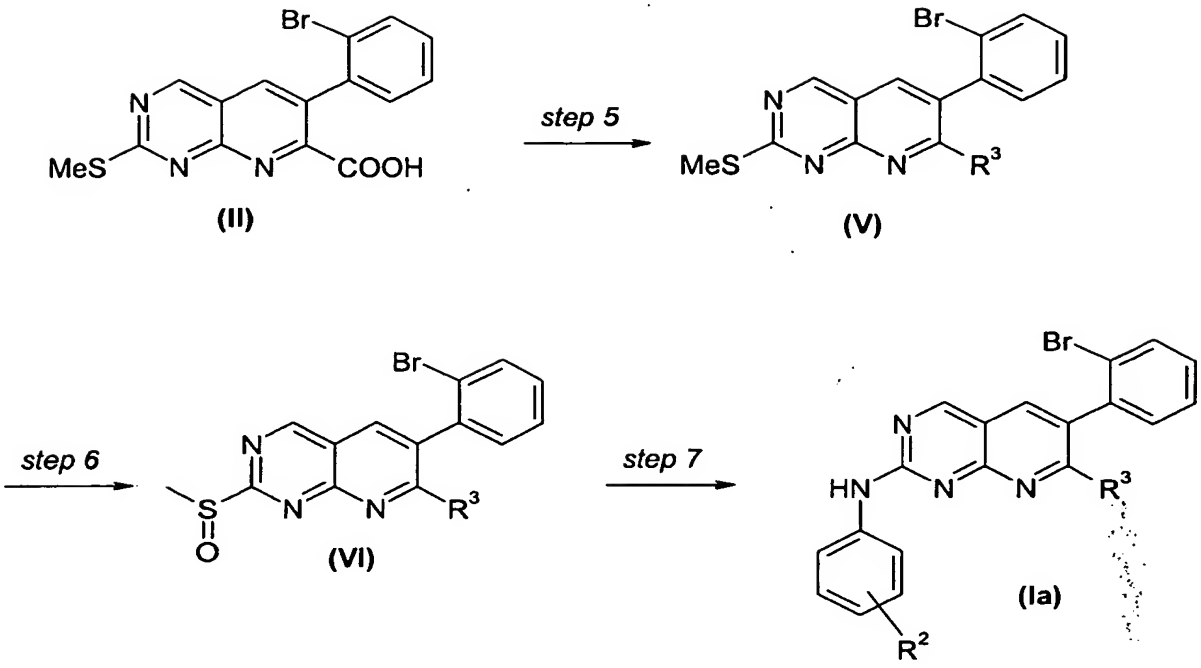
and R^2 has the significance given above.

Scheme 1



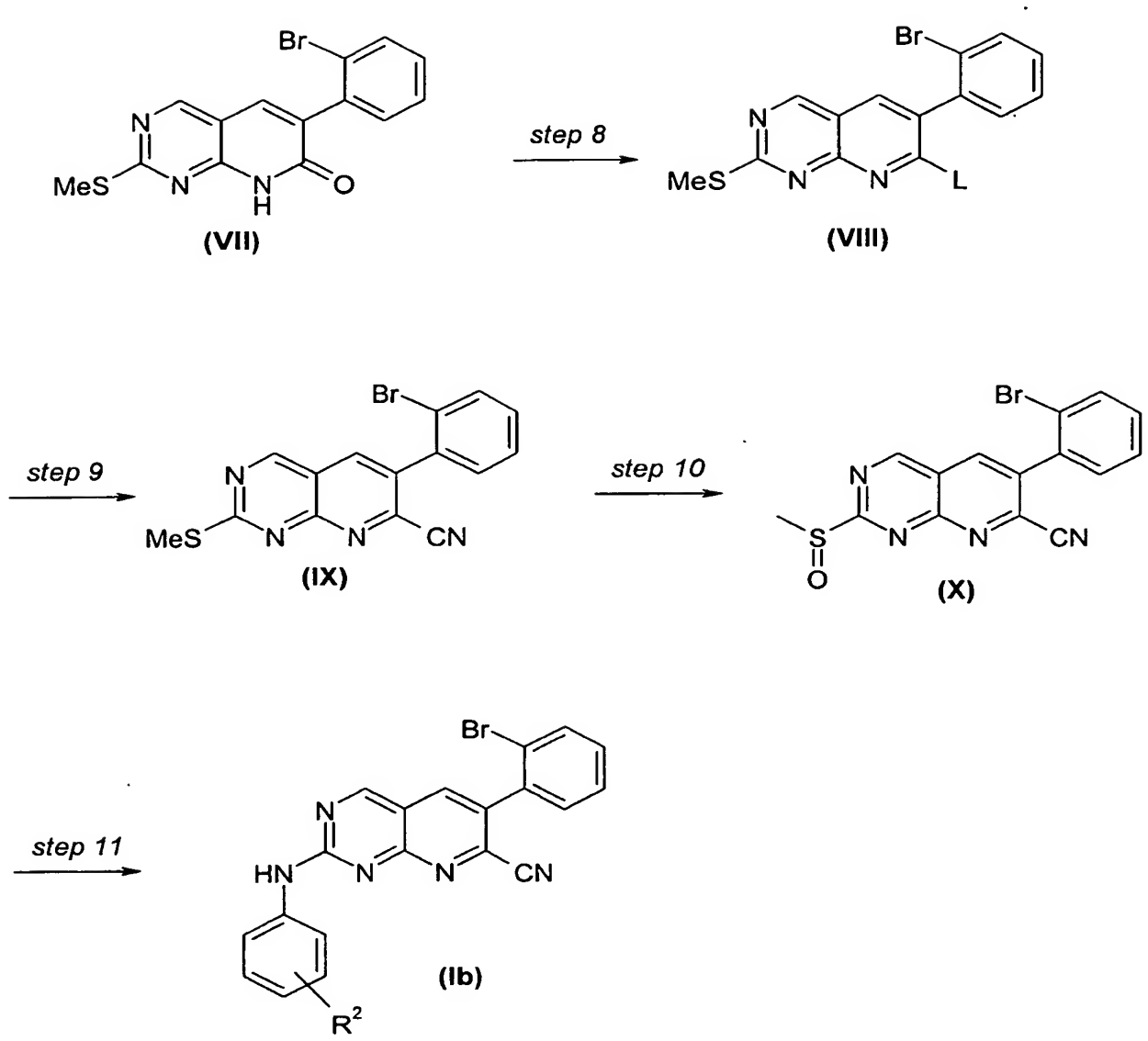
Alternatively, the carboxylic acids (II) can first be converted to carboxamides (V) and subsequently substituted by anilins on position 2 according to scheme 2, wherein R^3 and R^2 have the significance given above.

Scheme 2



Primary carboxamides of the formulae (Ia) or (V), wherein R^3 is $-C(O)-NH_2$, can be converted into nitriles of the general formula (Ib) by conventional methods, e.g. dehydration with $SOCl_2$ or $POCl_3$. Said nitriles of formula (Ib) may also be prepared from known pyridones (VII) according to scheme 3, wherein R^2 has the significance given herein before and L is a suitable leaving group.

Scheme 3



Step 1: 3-(2-bromo-phenyl)-pyruvic acid of formula (B), or in general arylpyruvic acids, can be condensed with a suitable pyrimidine carbaldehyde of formula (A) to give compound (II). Said condensation reaction can be performed under basic conditions, e.g with sodium hydroxide (NaOH) in water or methanol (MeOH) or 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) or potassium tert-butoxylate (KOtBu) in dimethyl formamide (DMF), 1-Methyl-2-pyrrolidinone (NMP) or tetrahydrofuran (THF). Alternatively, the condensation reaction is performed in

acetic acid in the presence of sodium acetate. Reaction temperatures range from room temperature (RT) to 150 °C.

Steps 2, 6 and 10:

A methylthio or alternatively any other alkylthio or arylthio group on position 2 of the pyridopyrimidines of formulae (II), (V) or (IX) can be converted into a suitable leaving group by oxidation to the corresponding sulfone or sulfoxide of the formulae (III), (VI) or (X). Suitable reagents are for instance 3-Chloroperoxybenzoic acid (mCPBA) or 2-benzenesulfonyl-3-phenyl-oxaziridine in inert solvents like dichlormethane (CH_2Cl_2), chloroforme ($CHCl_3$), or MTBE at temperatures ranging from –40 °C to + 65 °C .

Steps 3, 7, and 11:

The sulfoxides or sulfones from steps 2, 6 or 10 can be reacted in purified form or as crude products with anilines to give 2-anilino substituted pyridopyrimidines of the formulae (IV), (Ia, scheme 2) or (Ib). The reaction may be performed in excess aniline as the solvent or in an inert solvent like CH_2Cl_2, toluene, acetonitrile, DMF, dimethyl sulfoxide (DMSO) or NMP, and at temperatures in the range from 0 °C to 150 °C. Acids like trifluoroacetic acid (TFA) or hydrochloric acid (HCl) may be added to catalyze the reaction. If mCPBA has been used for the previous oxidation step, the formed m-chlorobenzoic acid present in the crude reaction mixture may serve as the catalyst.

Steps 4 and 5:

The appropriate carboxylic acids of formulae (IV) or (II, scheme 2) can be converted into amide derivatives of the formulae (Ia, scheme 1) or (V) by standard procedures known in the art. For instance, the acid is first activated by reaction with a carbodiimide or carbonyl diimidazole or oxalyl chloride, and subsequently reacted without isolation with the appropriate substituted amine or ammonia. This reaction is best performed in an inert solvent like THF, CH_2Cl_2 or NMP at temperatures ranging from 0 °C to 150 °C.

Step 8:

A suitable leaving group "L" in (VIII) may be a triflat, which can be prepared from (VII) by reaction with Tf_2O or $PhN(Tf)_2$ in an inert solvent like THF or CH_2Cl_2 or NMP, in the presence of a base like NEt_3, pyridine, KOtBu, LDA, NaH, or K_2CO_3.

Another leaving group is a chlorine or bromine atom which can be introduced by halogenation of the pyridone with $POCl_3$ or $POBr_3$.

Step 9:

The leaving group "L" in (VIII) can be substituted by an inorganic cyanide like potassium cyanide (KCN), sodium cyanide (NaCN) or copper cyanide (CuCN) in an inert solvent like diglyme, DMF, NMP, or sulfolane at temperatures from RT to 180 °C , to give (IX). Preferably, this reaction can also be catalyzed by a transiton metal catalyst, e.g. a Pd- or Ni catalyst. In this case, also zinc cyanide ($Zn(CN)_2$) may be applied as the cyanide source.

Certain side chains in R^3 or R^2 may require protection during the reaction sequences. Here standard protection and deprotection procedures being well known in the art may be applied. For instance, primary and secondary amines can be applied in t-butoxycarbonyl (Boc) or benzyloxycarbonyl protected form and the protecting group can be removed as a last reaction step by treatment with an acid like HCl or TFA.

The compounds of the general formula I can contain one or several chiral centers and can then be present in a racemic or in an optically active form. The racemates can be separated according to known methods into the enantiomers. For instance, diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid. Alternatively separation of the enantiomers can also be achieved by using chromatography on chiral HPLC-phases which are commercially available.

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-

2. Add 50 mg compound, disperse with spatulum and vortex.
3. Add 2 ml gelatin solution (weight beads: gelatin solution = 2:1) and vortex.
4. Cap and wrap in aluminium foil for light protection.
5. Prepare a counter balance for the mill.
6. Mill for 4 hours, 20/s in a Retsch mill (for some substances up to 24 hours at 30/s).
7. Extract suspension from beads with two layers of filter (100 µm) on a filter holder, coupled to a recipient vial by centrifugation at 400 g for 2 min.
8. Move extract to measuring cylinder.
9. Repeat washing with small volumes(here 1 ml steps) until final volume is reached or extract is clear.
10. Fill up to final volume with gelatin and homogenise.

The above described preparation yields micro-suspensions of the compounds of formula I with particle sizes between 1 and 10 µm. The suspensions are suitable for oral applications and were used in the in vivo pharmacokinetic testings described below.

The activity of the compounds according to this invention as inhibitors for the src-family tyrosine kinases was shown by using the following assay.

SRC-Inhibitor-Assay Parameters:

<u>Reaction mixture:</u>		
ATP		5 µM
Peptide (Ro + Ja133-Ro):		10 µM
	Ja133-Ro	196 nM
	Ro	9.8 µM
PT66		230 ng/ml
<u>Assay buffer:</u>		4 mM MgCl2
		2 mM TCEP
		50 mM HEPES
		0,1 % Tween 20
		pH 7.3
<u>Enzyme:</u>		2.5 U/ml

addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Ansel, H., et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed., 1995, pp. 196 and 1456-1457.

The compounds according to this invention and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The above-mentioned pharmaceutical preparations can be obtained by processing the compounds according to this invention with pharmaceutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

A preferred pharmaceutical preparation was obtained by using the following procedure:

1. Weigh 4.0 g glass beads in custom made tube GL 25, 4 cm (the beads fill half of the tube).

Inhibitor: max. 25 µM
min. 0.42 nM

Material:

Eu-labelled phosphotyrosine antibody: - for Lck Cisbio Mab PT66-K,
- for Src EG&G Wallac PT66 Eu-W1024
(all commercially available).

Peptides: Ro: NH_2-A-E-E-E-I-Y-G-E-F-E-A-K-K-K-K-$CONH_2$,
and

Ja133-Ro: Ja133-G-Aminocaprylic acid-A-E-E-E-I-Y-G-E-F-E-A-K-K-K-K-$CONH_2$, wherein Ja133 is LightCycler-Red 640-N-hydroxy succinimide ester ;

whereby both peptides were synthesized by an optimized solid phase peptide synthesis protocol (Merrifield, Fed. Proc. Fed. Amer. Soc. Exp. Biol. 21 (1962) 412) on a Zinsser SMP350 peptide synthesizer. Shortly, the peptide was assembled on 160 mg (22.8 µmol scale) of a Rink-Linker modified polystyrene solid phase by repeatedly conjugating an twenty fold excess of aminoacids each protected by temporary piperidine labile Fmoc- and permanent acid labile tert-Bu-, BOC- and Otert-Bu-groups depending on the side chain function. The substrate sequence AEEEIYGEFEAKKKK was N-terminal additionally mounted with the spacer amino acids Aminocaprylic acid and Glycin. After cleavage of the N-terminal temporary protecting group the still attached and protected peptide was labeled with a 1.5 fold amount of LightCycler-Red 640-N-hydroxy succinimide ester (purchased by Roche Diagnostics GmbH) and triethylamine. After 3 hrs. the resin was washed with Dimethylformamide and Isopropanol until the eluates of the blue resin got colourless. The fully protected and labeled peptide was removed from the solid phase and released from the permanent protecting groups by treatment with a mixture of 80% trifluoracetic acid, 10% Ethanedithiol, 5% Thioanisol and 5% Water. The substrate was finally isolated by a preparative reverse phase HPLC

purification. The purification yielded 12.2 mg RP-HPLC single peak pure blue material (lyophilisate). The identity was proven by MALDI mass spectroscopy [2720.0].

Enzymes: Upstate Lck ($p56^{lck}$, active), Upstate Src ($p60^{c\text{-}src}$, partially purified) were purchased from UBI.

Time-resolved Fluorescence Assay: Reader: Perkin Elmer, Wallac Viktor 1420-040 multilabel counter; Liquid handling system: Beckman Coulter, Biomek 2000.

ATP, Tween 20, HEPES were purchased from Roche Molecular Biochemicals, $MgCl_2$ and $MnCl_2$ were purchased from Merck Eurolab, TCEP was purchased from Pierce, 384 Well low volume fluorescence plates was purchased from Falcon.

Assay Description:

At first the enzyme is pre-incubated for 15 min. at 15°C in aqueous solution with corresponding amounts of inhibitors according to this invention. Then the phosphorylation reaction is started by adding a reaction mixture, containing ATP, Peptide and PT66, and subsequent shaking. The proceeding of this reaction is immediately monitored using time resolved fluorescence spectroscopy in a suitable well plate reader.

The IC_{50}-values can be obtained from the reaction rates by using a non-linear curve fit (Excelfit).

Ex-No.	Compound-Name	IC_{50} src [μM]	IC_{50} lck [μM]
1	6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-4-ylamide	0.0107	0.0601
2	6-(2-Bromo-phenyl)-2-(3-methanesulfonyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile	0.033	0.1589

Ex-No.	Compound-Name	IC_{50} src [μM]	IC_{50} lck [μM]
3-1	6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide	0.003	0.023
3-2	6-(2-Bromo-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide	0.0044	0.0125
3-3	6-(2-Bromo-phenyl)-2-(3-methylsulfanyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide	0.0078	
3-4	6-(2-Bromo-phenyl)-2-(4-sulfamoyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide	0.0069	0.0738
3-5	6-(2-Bromo-phenyl)-2-(3-methylsulfamoylmethyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide	0.0357	0.1101
3-6	6-(2-Bromo-phenyl)-2-[3-(2-hydroxy-ethanesulfonyl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide	0.0225	0.1453
3-7	6-(2-Bromo-phenyl)-2-(3-methanesulfonyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide	0.0166	0.1126
3-8	6-(2-Bromo-phenyl)-2-(3-methylsulfanyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide	0.0017	0.0323
3-9	6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide	0.0009	0.0121
3-10	6-(2-Bromo-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide	0.0016	0.0037
3-11	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-4-ylamide	0.0661	0.7742

Ex-No.	Compound-Name	IC_{50} src [µM]	IC_{50} lck [µM]
3-12	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide	0.0341	0.3497
3-13	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methoxy-ethyl)-amide	0.1141	0.3603
3-14	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-dimethylamino-propyl)-amide	0.0217	0.233
3-15	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-dimethylamino-2,2-dimethyl-propyl)-amide	0.0415	0.2177
3-16	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-acetylamino-ethyl)-amide	0.0814	0.1893
3-17	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methylamino-ethyl)-amide	0.0062	0.0398
3-18	1-[6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonyl]semicarbazide	0.0248	0.0684
3-19	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide	0.2003	0.3572
3-20	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid carbamoylmethyl-amide	0.0624	0.289
3-21	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1-methyl-piperidin-4-yl)-amide	0.0962	0.6377

Ex-No.	Compound-Name	IC_{50} src [μM]	IC_{50} lck [μM]
3-22	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-morpholin-4-yl-ethyl)-amide	0.158	0.6618
3-23	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-1-methyl-ethyl)-amide	0.1949	0.5727
3-24	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid methylcarbamoylmethyl-amide	0.1305	0.2055
3-25	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide	0.1572	0.3703
3-26	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide	0.197	0.2751
3-27	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-propyl)-amide	0.0239	0.1288
3-28	(S)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid pyrrolidin-3-ylamide	0.0193	0.0627
3-29	(R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid pyrrolidin-3-ylamide	0.103	0.4293
3-30	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid dimethylcarbamoylmethyl-amide	0.2467	0.1506
3-31	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-methylamino-propyl)-amide	0.0428	0.1003

Ex-No.	Compound-Name	IC_{50} src [μM]	IC_{50} lck [μM]
3-32	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-morpholin-4-yl-propyl)-amide	0.1168	0.1955
3-33	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amide	0.0447	0.0969
3-34	(R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-3-ylamide	0.0979	0.1269
3-35	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1-aza-bicyclo[2.2.2]oct-3-yl)-amide	0.0731	0.2507
3-36	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(pyridin-2-ylamino)-ethyl]-amide	0.1650	0.2555
3-37	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-sulfamoyl-ethyl)-amide	0.0210	0.1889
3-38	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-hydroxy-propyl)-amide	0.0918	0.4561
3-39	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(3H-imidazol-4-yl)-ethyl]-amide	0.0243	0.1137
3-40	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfinyl-ethyl)-amide	0.1486	0.5836
3-41	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1,5-dimethyl-1H-pyrazol-3-ylmethyl)-amide	0.0260	0.1260

Ex-No.	Compound-Name	IC_{50} src [μM]	IC_{50} lck [μM]
3-42	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (4-carbamoyl-1H-pyrazol-3-yl)-amide	0.0563	0.6938
3-43	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(2-hydroxy-ethanesulfinyl)-ethyl]-amide	0.1289	0.8090
3-44	6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methylamino-ethyl)-amide	0.001	0.0025
3-45	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide	0.0215	0.1554
3-46	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid N'-(2-dimethylamino-acetyl)-hydrazide	0.0168	0.0381
3-47	(S)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-3-ylamide	0.0066	0.0275
3-48	(R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (pyrrolidin-2-ylmethyl)-amide	0.0021	0.0381
3-49	6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1H-pyrazol-3-yl)-amide	0.0043	0.0073
4-1	6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile; compound with trifluoro-acetic acid	0.0065	0.0201
4-2	6-(2-Bromo-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile	0.0018	0.0051

Ex-No.	Compound-Name	IC_{50} src [µM]	IC_{50} lck [µM]
4-3	6-(2-Bromo-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile	0.0045	0.0499
4-4	6-(2-Bromo-phenyl)-2-[4-(2-ethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile	0.0011	0.0042
4-5	6-(2-Bromo-phenyl)-2-(3-methanesulfinyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile	0.0035	0.0521
4-6	6-(2-Bromo-phenyl)-2-[3-(2-hydroxy-ethanesulfonyl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile	0.0162	0.0997

In vivo assay on tumor inhibition:

To generate primary tumors, HT-29 colon carcinoma cells ($2.5x10^6$ in a volume of 100µl) were injected subcutaneously into the left flank of female SCID mice using a 1 ml syringe and a 26G needle. The HT-29 cells were originally obtained from the NCI and deposited in a working cell bank. The cells were thawed and expanded in vitro before use in the experiment. Mice were assigned to the treatment groups on day 9. For grouping (n = 12 mice per group), the animals were randomized to get a similar mean primary tumor volume of ca. 120 mm^3 per group. The test compounds were administered orally once per day as a suspension in 7.5% gelatine 0,22% NaCl with an administration volume of 10 ml/kg based on actual body weights. Treatment was initiated on day 10, and carried out until day 30, the final day of the study. The subcutaneous primary tumors were measured twice weekly, starting on day 7 after tumor cell implantation, in two dimensions (length and width) using an electronic caliper. The volume of the primary tumor was calculated using the formula: $V[mm^3]$ = (length [mm] x width [mm] x width [mm])/2.. In addition, the body weight of all animals was recorded at least twice weekly. Finally, at the end of the study the tumors were explanted and weighed.

The following examples, references are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit of the invention.

1) Starting materials

Example a

6-(2-Bromo-phenyl)-2-methylsulfanyl-pyrido[2,3-d]pyrimidine-7-carboxylic acid

3.372 g 3-(2-bromophenyl)2-oxopropionic acid in 20 ml DMF were treated with 4.434 g DBU under cooling and stirred for 10 min at RT. 2.728 g 4-amino-2-methylsulfanylpyrimidine-5-carbaldehyde were added and the mixture was stirred at 85 °C for 4.5 hrs. Stirring was continued over night at RT, then the solvent was evaporated and the residue dispensed in aqueous sodium carbonate solution. The mixture is extracted with ethyl acetate, then acidified to pH 2 and again extracted with chloroform. The chloroform extracts were dried and evaporated and the residue triturated with hot ethyl acetate. 2.786 g of the title product were thus obtained after filtration.

Example b

6-(2-Bromo-phenyl)-2-methylsulfinyl-pyrido[2,3-d]pyrimidine-7-carboxylic acid

1 g of 70% mCPBA were dissolved in 20 ml methylene chloride and dried by filtration over sodium sulfate. This solution was added dropwise to a solution of 1g of the compound from ex. a in 50 ml methylene chloride at RT. Stirring was continued for 2hrs and the resulting mixture used directly for the next step.

Example c

6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid

The crude solution from ex. b was treated directly with 0.325 g p-F-aniline and heated to reflux for 5 hrs. The solvent was evaporated and the residue purified by chromatography on silica, CH_2Cl_2 / MeOH eluent. Product containing fractions were concentrated and the residue triturated with a small amount of methanol.

Yield 0.712 g of the title product.

Example d

Trifluoromethanesulfonic acid 6-(2-bromo-phenyl)-2-methylsulfanyl-pyrido[2,3-d]pyrimidin-7-yl ester

To a suspension of 0.43 mg 55% sodium hydride in 15 ml NMP were added 3.0 g of 6-(2-Bromo-phenyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one in portions at RT. Stirring was continued at 40 °C for 30 min, then the solution was cooled to RT and 5.85 g of N-phenyl-bis(trifluoromethanesulfonimide) were added. After 30 min stirring at RT, the solvent was evaporated and the residue purified by flash chromatography (silica, ethylacetate / hexanes) to give 3.85 g of the title product.

Example e

6-(2-Bromo-phenyl)-2-methylsulfanyl-pyrido[2,3-d]pyrimidine-7-carbonitrile

1.95 g triflate from ex. d, 1.31 g tetrakis-(triphenylphosphino) palldium (0) and 0.381 g zinc cyanide were mixed in 20 ml NMP and stirred at 80 °C for 1 hr. Another 0.2 g catalyst were added and stirring continued for 2hr45. The NMP was removed by vacuum distillation and the residue chromatographed on silica (ethyl acetate / hexanes).

Yield 0.60 g of the title product.

Example f

6-(2-Bromo-phenyl)-2-methylsulfanyl-pyrido[2,3-d]pyrimidine-7-carboxamide

0.509 g carboxylic acid from ex. a and 0.15 g triethyl amine were dissolved in 10 ml THF. At –50 C, 1.0 ml ethyl chloroformiate (10 equivalents) were added and the mixture stirred for 30 min. 150 ml conc. aqueous ammonia were added and the mixture allowed to warm up to room temperature. The mixture was worked up with ethyl acetate and water, the water phases were extracted with chloroform and the organic phases concentrated and purified by chromatography on silica (ethyl acetate / hexanes).

Yield 0.28 g of the title product.

Final Products

Example 1

6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-4-ylamide

62 mg 6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid were dissolved in 2 ml DMF. At RT 27 mg 4-Amino-piperidine-1-carboxylic acid tert-butyl ester, 16 mg 1-hydroxybenzotriazole, and finally 26 mg 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added and the mixture heated to 50 °C. After 5 hrs the sovent was evaporated and the residue worked up with water and chloroform. The chloroform extracts were purified by chromatography over silica.

44 mg of this product were deprotected by stirring in 2 ml ethanol with 0.4 ml of a 2 M solution of HCl in ether. After 1 night at RT the mixture was evaporated and diluted with aqueous sodium carbonate solution. Extraction with ethyl acetate and further purification by chromatography (silica, $CHCl_3$/MeOH/NH_3 eluent) yielded 15 mg of the title product as a slightly yellow powder.

1H-NMR (CDCl3, ppm): 1.45 (m, 2H), 1.93 (m, 2H), 2.63 (m, 2H), 3.03 (broad d, 2H), 3.10 (t, 4H), 3.82 (t, 4H), 3.87 (m, 1H), 6.92 (d, 2H), 7.26 (m, overlap with CHCl3), 7.28 (m, 1H), 7.34 (m, 1H), 7.46 (s, 1H), 7.55 (d, 1H), 7.57 (broad signal, 2H), 7.88 (s, 1H), 7.93 (broad d, 1H), 9.07 (s, 1H).

Example 2

6-(2-Bromo-phenyl)-2-(3-methanesulfonyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile

60 mg of the starting material from ex. e in 3 ml chloroform were treated with 0.22 g 2-benzenesulfonyl-3-phenyl-oxaziridine at RT for 5 hrs. Excess oxidizing reagent was destroyed by addition of 52 mg dimethylsulfide and stirring for additional 75 min. Finally 0.244 g 3-methylsulfonylaniline hydrochloride were added and the mixture was stirred for 1 day at RT. 5 ml NMP were added and stirring continued for one more day. The mixture was diluted with water, the organic phase separated and washed with water. The organic phase was concentrated and the residue stirred

with a mixture of 10 ml methanol and 5 water. Filtration yielded 42 mg of the title product as a pale yellow powder.

1H-NMR (DMSO-d6, ppm): 3.20 (s, 3H), 7.49 (m, 1H), 7.55- 7.70 (m, 4H), 7.84 (d, 1H), 8.35 (broad d, 1H), 8.55 (broad s, 1H), 8.63 (s, 1H), 9.57 (s, 1H), 10.92 (s, 1H).

Example 3

According to the synthesis procedure described in Example 1 and using the corresponding starting materials, the following compounds can be obtained:

3-1 6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide

3-2 6-(2-Bromo-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide

3-3 6-(2-Bromo-phenyl)-2-(3-methylsulfanyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide

3-4 6-(2-Bromo-phenyl)-2-(4-sulfamoyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide

3-5 6-(2-Bromo-phenyl)-2-(3-methylsulfamoylmethyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide

3-6 6-(2-Bromo-phenyl)-2-[3-(2-hydroxy-ethanesulfonyl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide

3-7 6-(2-Bromo-phenyl)-2-(3-methanesulfonyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid amide

3-8 6-(2-Bromo-phenyl)-2-(3-methylsulfanyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide

3-9 6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide

3-10 6-(2-Bromo-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide

3-11 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-4-ylamide

3-12 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-amide

3-13 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methoxy-ethyl)-amide

3-14 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-dimethylamino-propyl)-amide

3-15 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-dimethylamino-2,2-dimethyl-propyl)-amide

3-16 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-acetylamino-ethyl)-amide

3-17 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methylamino-ethyl)-amide

3-18 1-[6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonyl]semicarbazide

3-19 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide

3-20 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid carbamoylmethyl-amide

3-21 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1-methyl-piperidin-4-yl)-amide

3-22 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

3-23 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-1-methyl-ethyl)-amide

3-24 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid methylcarbamoylmethyl-amide

3-25 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide

3-26 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide

3-27 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-dimethylamino-propyl)-amide

3-28 (S)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid pyrrolidin-3-ylamide

3-29 (R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid pyrrolidin-3-ylamide

3-30 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid dimethylcarbamoylmethyl-amide

3-31 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-methylamino-propyl)-amide

3-32 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-morpholin-4-yl-propyl)-amide

3-33 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amide

3-34 (R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-3-ylamide

3-35 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1-aza-bicyclo[2.2.2]oct-3-yl)-amide

3-36 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(pyridin-2-ylamino)-ethyl]-amide

3-37 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-sulfamoyl-ethyl)-amide

3-38 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (3-hydroxy-propyl)-amide

3-39 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(3H-imidazol-4-yl)-ethyl]-amide

3-40 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methanesulfinyl-ethyl)-amide

3-41 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1,5-dimethyl-1H-pyrazol-3-ylmethyl)-amide

3-42 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (4-carbamoyl-1H-pyrazol-3-yl)-amide

3-43 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid [2-(2-hydroxy-ethanesulfinyl)-ethyl]-amide

3-44 6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methylamino-ethyl)-amide

3-45 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-hydroxy-ethyl)-amide

3-46 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid N'-(2-dimethylamino-acetyl)-hydrazide

3-47 (S)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid piperidin-3-ylamide

3-48 (R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (pyrrolidin-2-ylmethyl)-amide

3-49 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (1H-pyrazol-3-yl)-amide

3-50 6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2-methyl-2H-pyrazol-3-yl)-amide

3-51 (S)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2,3-dihydroxy-propyl)-amide

3-60 (R)-6-(2-Bromo-phenyl)-2-(4-fluoro-phenylamino)-pyrido[2,3-d]pyrimidine-7-carboxylic acid (2,3-dihydroxy-propyl)-amide

Example 4

According to the synthesis procedure described in Example 2 and using the corresponding starting materials, the following compounds can be obtained:

4-1 6-(2-Bromo-phenyl)-2-(4-morpholin-4-yl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile; compound with trifluoro-acetic acid

4-2 6-(2-Bromo-phenyl)-2-[4-(2-diethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile

4-3 6-(2-Bromo-phenyl)-2-[4-(2-hydroxy-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile

4-4 6-(2-Bromo-phenyl)-2-[4-(2-ethylamino-ethoxy)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile

4-5 6-(2-Bromo-phenyl)-2-(3-methanesulfinyl-phenylamino)-pyrido[2,3-d]pyrimidine-7-carbonitrile

4-6 6-(2-Bromo-phenyl)-2-[3-(2-hydroxy-ethanesulfonyl)-phenylamino]-pyrido[2,3-d]pyrimidine-7-carbonitrile

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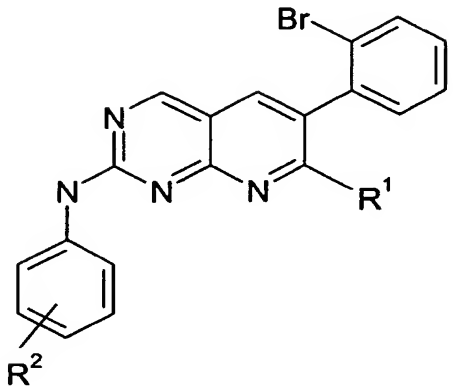
Patent Claims

1. The compounds of formula I



(formula I),

wherein

R^1 is -C(O)-NH-alkyl or -C(O)-N(alkyl)$_2$, which alkyl groups are optionally substituted with

-OH;
-NH(alkyl);
-N(alkyl)$_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-N(alkyl)$_2$;
-C(O)-NH$_2$;
-O-alkyl;
-heterocyclyl;
-NH-heterocyclyl;
-S(O)$_2$-NH$_2$; or
-S(O)-alkyl, which alkyl is optionally substituted with -OH;

or a group

-CN;
-C(O)-NH$_2$;

-C(O)-NH-heterocyclyl;
-C(O)-NH-NH-C(O)-NH_2; or
-C(O)-NH-NH-C(O)-alkyl, which alkyl is optionally substituted with
-NH(alkyl); or
-N(alkyl)$_2$; and

R^2 is halogen;
heterocyclyl;
-$(CH_2)_m$-S(O)$_2$-NH_2;
-$(CH_2)_m$-S(O)$_2$-N(alkyl)$_2$; or
-$(CH_2)_m$-S(O)$_2$-NH-(alkyl);
-O-alkyl; or
-S(O)$_n$-alkyl, which alkyl groups are optionally substituted by
-OH;
-O-(C_1-C_4)alkyl;
-NH-alkyl; or
-N(alkyl)$_2$;

m is 0, 1, 2, 3, 4, 5 or 6;
n is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

2. The compounds according to claim 1, wherein

R^2 is halogen;

and pharmaceutically acceptable salts thereof.

3. The compounds according to claim 1, wherein

R^2 is morpholin-4-yl;
-S-alkyl; or a group
-O-alkyl, which alkyl group is substituted with
-N(alkyl)$_2$;

and pharmaceutically acceptable salts thereof.

4. The compounds according to claim 1 or 3, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is substituted with
-OH;
-NH(alkyl);
-N(alkyl)$_2$; or
-S(O)$_2$-NH$_2$;

or a group

-C(O)-NH-piperidin-3-yl;
-C(O)-NH-pyrrolidin-3-yl; or
-C(O)-NH-(CH$_2$)$_2$-imidazol-4-yl; and

R^2 is morpholin-4-yl;
-S-alkyl; or a group
-O-alkyl, which alkyl group is substituted with
-N(alkyl)$_2$;

and pharmaceutically acceptable salts thereof.

5. The compounds according to claim 1 or 2, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is optionally substituted with
-OH;
-NH(alkyl);
-N(alkyl)$_2$;
-NH-C(O)-alkyl;
-C(O)-NH-alkyl;
-C(O)-N(alkyl)$_2$;
-C(O)-NH$_2$;
-O-alkyl;

-S(O)-alkyl, which alkyl is optionally substituted with -OH; or
-$S(O)_2$-NH_2; and

R^2 is halogen;

and pharmaceutically acceptable salts thereof.

6. The compounds according to claim 1 or 2, wherein

R^1 is -C(O)-N(CH_3)alkyl, which alkyl group is optionally substituted with
-NH(alkyl);
-N(alkyl)$_2$; and

R^2 is halogen;

and pharmaceutically acceptable salts thereof.

7. The compounds according to claim 1 or 2, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is substituted with
morpholin-4-yl;
pyrrolidinyl;
2-oxo-imidazolidinyl;
2-oxo-pyrrolidinyl;
1-methyl-pyrrolidinyl;
3H-imidazolyl;
1,5-dimethyl-pyrazolyl; or
-NH-pyridinyl;

R^2 is halogen;

and pharmaceutically acceptable salts thereof.

8. The compounds according to claim 1, wherein

R^1 is -C(O)-NH-alkyl, which alkyl group is substituted with
-NH-alkyl;
-N(alkyl)$_2$; or a group
-C(O)-NH-piperidin-4-yl; and

R^2 is morpholin-4-yl;
-S-alkyl; or a group
-O-alkyl, which alkyl group is substituted with
-N(alkyl)$_2$;

and pharmaceutically acceptable salts thereof.

9. The compounds according to claim 1 or 2, wherein

R^1 is -C(O)-NH-heterocyclyl;
-C(O)-NH-NH-C(O)-NH$_2$; or
-C(O)-NH-NH-C(O)-alkyl, which alkyl is optionally substituted with
-NH(alkyl); or
-N(alkyl)$_2$;

R^2 is halogen;

and pharmaceutically acceptable salts thereof.

10. The compounds according to claim 1, wherein

R^1 is -C(O)-NH$_2$; and
R^2 is morpholin-4-yl;
-$(CH_2)_m$-S(O)$_2$-NH-(alkyl);
-$(CH_2)_m$-S(O)$_2$-NH$_2$; or a group
-O-alkyl, -S(O)$_n$-alkyl, which alkyl groups are optionally substituted by
-OH;
-NH-alkyl; or

-N(alkyl)$_2$;

m is 0, 1, 2, 3, 4, 5 or 6;
n is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

11. The compounds according to claim 1, wherein

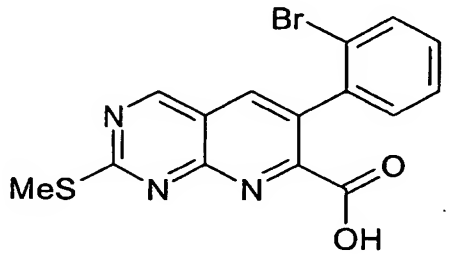
R^1 is -CN; and
R^2 is morpholin-4-yl;
-S(O)$_n$-alkyl; or a group
-O-alkyl, which alkyl group is optionally substituted by
-OH;
-NH-alkyl;
-N(alkyl)$_2$;

n is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

12. A process for the manufacture of the compounds according to claim 1, wherein

(a) the sulfide group in the compounds of the general formula (II)



formula (II),

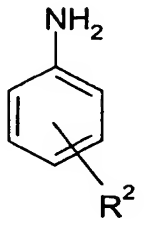
is converted into the corresponding sulfoxide group, which sulfoxide group is

13. A medicament containing one or more compounds according to any of the claims 1 to 11 as active ingredients together with pharmaceuticaly acceptable adjuvants.

14. A medicament according to claim 13 for the treatment of cancer.

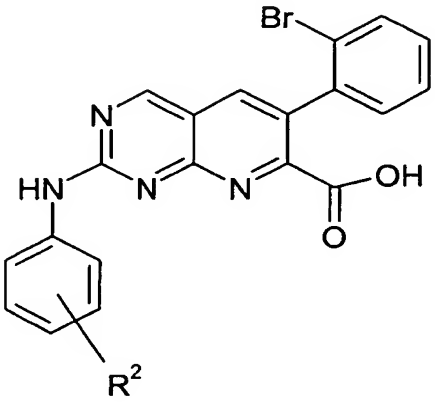
15. The use of one or more compounds according to any of the claims 1 to 11 for the treatment of cancer.

(b) substituted by the respective anilines of formula (II-A)



formula (II-A)

wherein R^2 has the meaning given in claim 1, to give the compounds of the general formula (IV)



formula (IV),

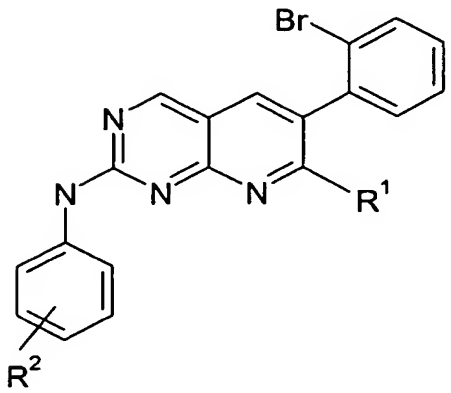
(c) the -COOH group in formula (IV) is converted into an amide derivative of formula (I); and

(d) if desired a primary amide derivative obtained from (c) is further converted into its corresponding 7-carbonitril derivative of formula (I); and

(e) if desired said compound of the general formula (I), obtained from (c) or (d), is converted into a pharmaceutically acceptable salt.

Abstract

The invention describes compounds of the general formula I



formula (I),

a process for their manufacture, medicaments containing them and their manufacture as well as the use of these compounds as pharmaceutically active agents. The said compounds show activity as protein kinase inhibitors, in particular src family tyrosine kinase inhibitors, and may therefore be usefull for the treatment of diseases mediated by said tyrosine kinases.

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